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# Evidence for Deficiencies in Perceptual and Semantic Olfactory Processes in Parkinson's Disease

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## Abstract

Olfactory deficits have been reported in Parkinson's disease (PD) and are thought to represent a sensitive marker of the disease. The aim of the present study was to examine the differential contribution in olfactory dysfunction of perceptual and semantic processes of odours in PD patients. Twenty-four PD patients (12 males and 12 females) and 24 control subjects (12 males and 12 females) were tested. The experiment included two sessions. Initially, 12 odorants were delivered, one per minute. For each odour, subjects were asked to rate intensity, pleasantness, familiarity and edibility using linear rating scales. The odorants were again presented and the subjects were asked to identify them. The four olfactory judgements and odour identification were severely disturbed in PD patients when compared to control subjects. These findings demonstrate major deficits for all cognitive tasks of olfactory judgement in PD, and suggest that PD is associated with disruption of olfactory areas situated in the temporal lobes and also in the prefrontal cortex.

**Key words**: olfaction, Parkinson's disease, perceptual and semantic processes

## Introduction

Olfactory dysfunction is frequently reported in patients with idiopathic Parkinson disease (PD) and represents a sensitive marker for this illness (Doty *et al*., 1992b). Olfactory deficits in PD patients are evidenced using different types of tasks such as odour detection, discrimination, recognition memory and identification (Ansari and Johnson, 1975; Ward *et al*., 1983; Korten and Meulstee, 1980; Corwin *et al*., 1985; Serby *et al*., 1985a,b; Quinn *et al*., 1987; Doty *et al*., 1988; Zucco *et al*., 1991; Busenbark *et al*., 1992; Mesholam *et al*., 1998; Potagas *et al*., 1998; Daum *et al*., 2000; Tissingh *et al*., 2001). Using the University of Pennsylvania Smell Identification Test (UPSIT), deficits in odour identification are general and not restricted to any subset of odorants (Doty *et al*., 1988). Olfactory dysfunction is further found to be bilateral and independent of gender, disease duration, medication, motor disability, and functions related to cognitive, perceptivo-motor and memory skills (Doty *et al*., 1988, 1989, 1992b). Olfactory dysfunction can be partly explained by damage in the initial part of the olfactory pathway, since anatomical abnormalities, known as Lewy bodies, are observed in the olfactory bulb and notably in the anterior olfactory nucleus (Daniel and Hawkes, 1992; Hawkes *et al*., 1997; Liberini *et al*., 1999; Del Tredici *et al*., 2002).

In two recent studies on patients with Alzheimer's disease (AD) or schizophrenia (Royet *et al*., 2001b; Hudry *et al*., 2002), we used an original test allowing rapid and accurate assessment of different olfactory judgements. In a first session, the subjects were asked to successively make intensity, pleasantness, familiarity and edibility judgements of 12 odorants using linear rating scales, and, in a second session, to identify these same odorants, using a list of five alternative odour names. Based on cognitive psychology concepts (Craik and Lockhart, 1972; Craik and Tulving, 1975; Schab, 1991; Kosslyn and Koenig, 1992), we suggested that intensity, familiarity, pleasantness and edibility judgements could represent different olfactory judgements performed by subjects while identifying odours, from perceptual to semantic representations. We assumed that perceptual and semantic odour representations are stored in separate neural subsystems and claimed that not only familiarity but also intensity and hedonicity decisions can be primarily performed with the activation of a perceptual odour representation,

**Table 1** List and order of the odorants presented for the two sessions

| No. | Veridical name | Chemical name | Dilution in % | Distractor names | | | |
|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | 3 | 4 |
| 1 | Mushroom | 1-octen-3-ol | 1 | mould | camphor | liquorice | lilac |
| 2 | Lemon | mixture | 1 | hyacinth | grapefruit | vanilla | apricot |
| 3 | Vinegar | acetic acid | 0.1 | orange | mustard | gardenia | cider |
| 4 | Lavender | mixture | 1 | incense | caramel | mothballs | thyme |
| 5 | Citronella | mixture | 1 | banana | lychee | tar | verbena |
| 6 | Clove | eugenol | 1 | lawn | garlic | chocolate | cinnamon |
| 7 | Ether | diethyl ether | 0.1 | chloroform | lily | pizza | nail varnish |
| 8 | Strawberry | mixture | 1 | biscuit | raspberry | petrol | passion fruit |
| 9 | Gas | tetrahydrothiophene | 0.1 | oil | carnation | cheese | turpentine |
| 10 | Mint | mixture | 1 | bitter almond | rose | liquorice | anise |
| 11 | Pine | mixture | 1 | eucalyptus | wax | tobacco | gingerbread |
| 12 | Smoked salmon | mixture | 1 | prawn | ham | glue | jonquil |

whereas edibility judgements would rather involve the activation of semantic odour representations (Royet *et al.*, 1999, 2001a,b). Although olfactory deficits have been reported for all the classic types of olfactory task (detection, recognition memory, identification, naming) in both Alzheimer and schizophrenia patients, we observed a variable effect of these diseases on our olfactory judgement tasks. Whereas the olfactory deficit in AD was restricted to the familiarity judgement and identification, patients with schizophrenia were also found to have deficient hedonicity and edibility judgements and these could be gender dependent. These data suggest varied dysfunctional olfactory processes as a function of the disease. The aim of the present study was to examine PD patients' performances in these different tasks of olfactory judgement and to rate the differential contribution of olfactory dysfunction in perceptual and semantic processes of odours.

## Materials and methods

### Subjects

Twenty-four non-demented patients fulfilling the criteria for idiopathic PD (Gibb and Lees, 1988) were recruited in the Department of Neurology (Neurological Hospital of Lyon, France). There were 12 men and 12 women [respective age (mean ± SD) = 63.2 ± 8.3 and 67.5 ± 7.3 years]. The disease duration ranged from 2 to 10 years in males (mean ± SD = 7.0 ± 2.9 years) and from 4 to 18 years in females (mean ± SD = 10.9 ± 4.6 years). All the PD patients had received levodopa plus a peripheral decarboxylase inhibitor and had demonstrated a sustained response to the levodopa at follow-up. The mean daily levodopa dosage was 521 ± 262 mg (dose range 150–900 mg/day) in males and 817 ± 431 mg (range 150–1700 mg/day) in females. Most of these patients (18 out of 24) were taking dopaminergic agonists in addition to the levodopa, and a few of them were also taking selegiline, entacapone, amantadine or anticholinergics. Motor per- formance was assessed during dopaminergic treatment using the modified Hoehn and Yahr scale and part III of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn *et al.*, 1987). We therefore had a measure of patient disability while 'on medication'. The mean Hoehn and Yahr stage was 2.1 ± 0.4 in males and 2.4 ± 0.6 in females. The mean UPDRS motor score (max. score: 108) was 19.9 ± 8.5 (range 10–37) in males and 20.4 ± 9.3 (range 6–39) in females. Olfactory tests were performed immediately after motor examination.

PD patients were compared to 24 age-matched healthy control subjects that were either spouses of PD patients or recruited in retirement communities for elderly people. Control subjects were 12 males and 12 females with a mean age of 63.9 ± 6.4 years (range 51–73) and 66.9 ± 8.7 years (range 53–81), respectively. They had no significant neurological disease, brain damage or other medical problem. Exclusion criteria for both controls and PD patients were known anosmia or a current cold that could interfere with smell performance. The procedure was fully explained and informed consent sought before either PD patients or control subjects were included in the study.

### Stimuli

Twelve odorants (Table 1) were chosen from 185 odorants previously evaluated by a large number of subjects (Royet *et al.*, 1999). They were selected as being rather familiar, but strong or weak, pleasant or unpleasant, and edible or inedible. Seven odorants were supplied by Givaudan-Roure (France) or International Flavor and Fragrances (France) and consisted of mixtures of odorants (lemon, lavender, citronella, strawberry, mint, pine, smoked salmon). The five others (mushroom, clove, ether, vinegar and gas) were

obtained from simple chemical compounds (1-octen-3-ol, eugenol, diethyl ether, acetic acid and tetrahydrothiophene, respectively) and were provided by manufacturers of chemical products (Aldrich or Sigma, France).

Odorous products were contained in 15 ml yellow glass jars with screw lids in polypropylene (Fisher, Erlancourt, France). The jars were opaque to mask any visual cues as to identity. The odorants were diluted in mineral oil so that 5 ml of odorous solution (1%) was prepared and absorbed by compressed filaments of polypropylene. Because tetrahydrothiophene, acetic acid and ether released a very strong odour, they were diluted 1000 times. Odorants were kept in a refrigerator when not in use and were removed before the experiment began and left to reach room temperature.

### Experimental procedure

The whole experiment included two sessions. Before the first session, subjects were only given instructions concerning the tasks to be performed immediately. Twelve odorous stimuli were then delivered at the rate of one odorant per minute. Each odorant was presented for ~5 s. For each odour, the subjects were asked to successively rate the intensity, pleasantness, familiarity and edibility with linear 10 cm rating scales segmented and numbered from 1 to 10. To further indicate the degree of the judgement demanded, the scale extremities were marked 'very weak' and 'very strong', 'very unpleasant' and 'very pleasant', 'very unfamiliar' and 'very familiar', and 'very inedible' and 'very edible', for intensity, pleasantness, familiarity and edibility, respectively.

In the second session, the same 12 odorants were again presented in the same order and with the same inter-stimulus interval as in the first session. For each presented odorant, subjects had to identify odours by choosing a name among a written list of five alternative proposals that comprised the veridical label, one name evoking a similar odour and three names evoking more distinct odours, either edible or inedible (Table 1).

### Quantitative and statistical analyses

The scores obtained for intensity, pleasantness, familiarity and edibility were directly deduced from the value selected on the rating scales by each subject for each odour. The odour identification scores were determined by attributing the value '1' when the veridical label was selected, and the value '0' when one out of the four other alternative names indicated in Table 1 was chosen.

The intensity, pleasantness, familiarity and edibility judgements were considered as being different olfactory tasks, involving different olfactory processes. However, it has previously been shown that there are significant correlations between these tasks (Henion, 1971; Doty *et al.*, 1984; Distel *et al.*, 1999; Royet *et al.*, 1999). Therefore a multivariate analysis of variance (MANOVA) with group (patient vs. control), gender (male vs. female) and judgement type (intensity, hedonicity, familiarity, edibility) was performed with repeated measurements on the odorant factor. Analyses of variance (ANOVA) with repeated measurements (Winer, 1962) were then used to separately analyse the scores relative to the different olfactory judgement tasks. The differences between pairs or groups of means were assessed by multiple orthogonal contrasts. The normality of the samples and the homogeneity of their variance were controlled with the Lilliefors (Conover, 1971) and the Hartley (Winer, 1962) tests, respectively. Identification scores, classified dichotomously, were analysed with a logistic regression analysis (Kleinbaum *et al.*, 1988).

To compare the performances between olfactory tasks by suppressing the potential risk of differential task difficulty, a two-way ANOVA with repeated measurements was performed on patients' scores standardized as Z-scores using the control group means and standard deviations (Chapman and Chapman, 1978). Since data obtained for hedonic and edibility judgements present bipolar dimensions, this analysis only included deficits observed for the intensity, familiarity and identification tasks.

To investigate whether the PD patients' olfactory performances could be predicted by their demographic or clinical characteristics, Spearman rank-order correlations were performed between performances observed for each odour task, and age, duration of illness, scores at Hoehn and Yahr, scores at UPDRS III and daily levodopa doses.

## Results

### Olfactory performance

The arithmetic mean of the scores obtained for intensity, pleasantness, familiarity, edibility and identification were computed and are presented in Figure 1 as a function of the two groups of subjects (factor A: patient vs. control), gender (factor B: male vs. female) and the 12 odorants (factor C).

The MANOVA results showed a significant effect for the group [Wilks' $\lambda(11,166) = 5.62$; $P < 0.0001$], judgement [Wilks' $\lambda(33,490) = 7.70$; $P < 0.0001$], and odorant [Wilks' $\lambda(11,166) = 9.839$; $P < 0.0001$], but not sex [Wilks' $\lambda(11,166) = 1.420$; $P = 0.1678$] factors. Significant interactions between group and judgement [Wilks' $\lambda(33,490) = 1.646$; $P = 0.0147$], but not between group and gender [Wilks' $\lambda(11,166) = 1.608$; $P = 0.1006$], sex and judgement [Wilks' $\lambda(33,490) = 0.3977$; NS], and group, gender and judgement factors [Wilks' $\lambda(33,490) = 0.9176$; NS] were also observed. Univariate tests with two-way ANOVAS (groups × odorants) were then performed for these four olfactory tasks. Except for the edibility judgement, the ANOVAs showed that patient performances were significantly lower than those of the controls (Table 2). Logistic regression analysis gave predictions of correct over false identification scores (Table 3). The success rate in the classification of identification scores was 95.8%.

The ANOVA performed on standardised olfactory scores ($Z$-scores) revealed no significant effect of the olfactory task

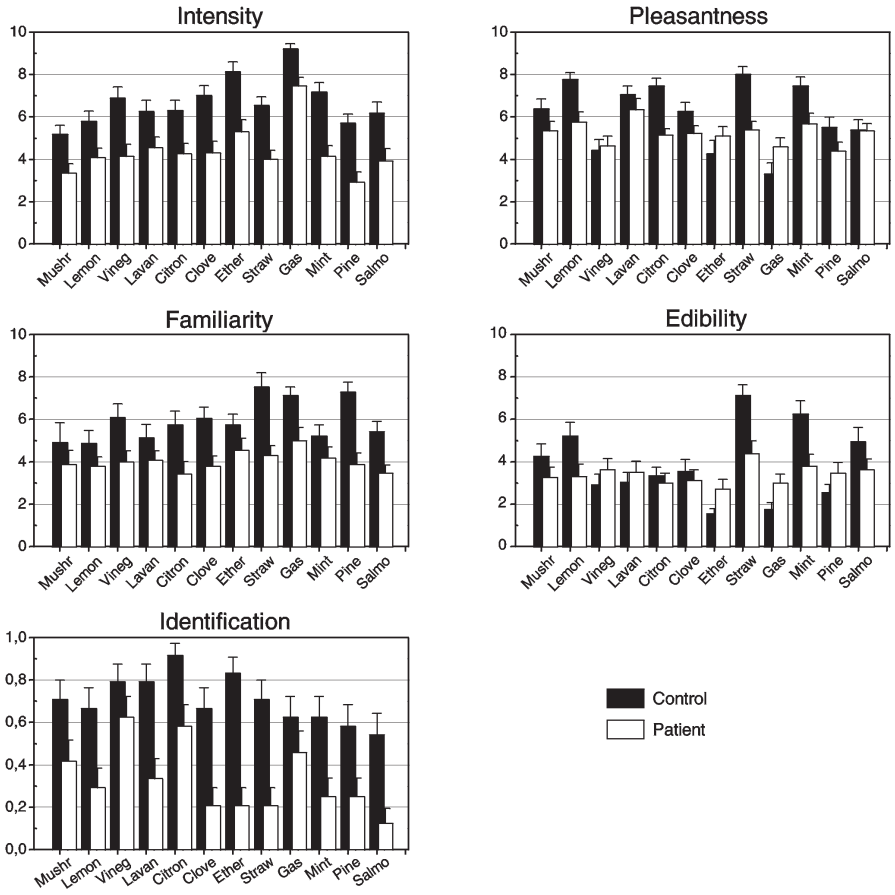


**Figure 1** Scores of intensity, pleasantness, familiarity, edibility, and identification as a function of the subject groups, and the 12 odorants.

**Table 2** Three-way ANOVAs performed on scores recorded from the tasks of intensity, pleasantness, familiarity and edibility judgements

| Factor | df | Intensity | | Pleasantness | | Familiarity | | Edibility | |
|---|---|---|---|---|---|---|---|---|---|
| | | *F* | *P* | *F* | *P* | *F* | *P* | *F* | *P* |
| Group | 1,46 | 41.242 | <0.0001 | 8.436 | 0.0056 | 21.593 | <0.0001 | 1.639 | NS |
| Odorants | 11,44 | 12.800 | <0.0001 | 10.751 | <0.0001 | 2.598 | 0.0032 | 10.017 | <0.0001 |
| Group × odorant | 11,484 | 0.678 | NS | 4.364 | <0.0001 | 1.640 | NS | 4.589 | <0.0001 |

[$F(2,69) = 2.435$, $P = 0.095$], but a significant effect of odorant factor [$F(11,759) = 4.867$, $P < 0.0001$] and a significant judgement × odorant interaction [$F(22,759) = 2.364$, $P = 0.0004$].

### Relation of demographic and clinical variables to olfactory performance

The mean age of subjects was compared as a function of group (patient vs. control) and gender (male vs. female). A two-way ANOVA showed no significant effects for group [$F(1,44) = 0.001$, NS] and gender [$F(1,44) = 2.70$, NS], nor any significant interaction between these two factors [$F(1,44) = 0.09$, NS].

Duration of illness, score at Hoehn and Yahr, score at UPDRS III and dose of levodopa were also compared between male and female PD. Significant gender differences were noted as a function of duration of illness [$F(1,22) = 6.17$, $P = 0.021$] and levodopa dosage [$F(1,22) = 4.12$, $P = 0.055$], but not for the Hoehn and Yahr score [$F(1,22) = 1.88$, NS] nor the UPDRS III score [$F(1,22) = 0.02$, NS].

Table 4 presents the within-group correlations between demographic/clinical variables and olfactory scores. Spearman rank-order correlations revealed only a few significant relations between olfactory scores and demographic and clinical variables. We mainly found significant, but weak, inverse correlations between several olfactory scores and gender, age and the Hoehn and Yahr scores.

## Discussion

The present study highlights the influence of PD on different odour processes. Although deficits in odour identification have already been reported in this neurological disease, this is the first study that simultaneously investigates the intensity, familiarity, pleasantness and edibility judgements and shows clear impairment of these four olfactory tasks in PD patients. The performances measured for these different olfactory tasks were independent of each other, except for those scored between intensity and pleasantness judgements. This therefore corroborates the findings showing that the dimensions of the intensity and pleasantness judgements are correlated (Henion, 1971; Doty *et al*., 1984; Distel *et al*., 1999; Royet *et al*., 1999), but within the framework of the present study this does not allow us to conclude that these two tasks involve different odour processes and, as a consequence, presupposes different olfactory neural networks.

Our data for the PD patients demonstrate severe olfactory dysfunction since they present markedly diminished performances for the intensity, pleasantness, familiarity and edibility judgements. These olfactory deficits could be due in part to peripheral dysfunction because PD patients are reported to have a diminished ability for odour detection compared to controls (Ansari and Johnson, 1975; Ward *et al*., 1983). It has been suggested that environmental agents could enter the brain through the olfactory nerves leading to injury of the olfactory nerves and subsequently the nigrostriatal neurons (Burns *et al*., 1983; Doty, 1991; Doty *et al*., 1991, 1992a; Stern *et al*., 1994), or that the olfactory dysfunction could be the result of the PD neurodegenerative process involving retrograde degeneration of the nasal epithelium and the olfactory bulb (Doty *et al*., 1991; Daniel and Hawkes, 1992; Stern *et al*., 1994; Hawkes *et al*., 1997; Liberini *et al*., 1999). It is also tempting to relate the clinical picture including olfactory deficits, with neurochemical and neuropathological features. Dopaminergic mesencephalic and cholinergic projections to the olfactory areas such as the olfactory bulb, the piriform cortex and the olfactory tubercle, are well established (Fallon and Moore, 1978; Dubois *et al*., 1990). An improved olfactory function was recently reported in two patients during transcranial application of low frequency AC pulsed electromagnetic fields (Sandyk, 1999). Smell recovery was supposedly related to small amounts of dopamine released into the synapse of the olfactory bulb inducing activation of postsynaptic dopamine D2 receptors. However, most studies have not shown any significant effect of dopaminergic and cholinergic manipulations on olfactory abilities (Korten and Meulstee, 1980; Ward *et al*., 1983; Quinn *et al*., 1987; Martzke *et al*., 1997; Liberini *et al*., 2000;). Neither has any correlation been found between olfactory function and

**Table 3** Prediction of identification scores from the logistic regression analysis

| No. | Variables | Odds ratio | 95% confidence intervals | *P* |
|---|---|---|---|---|
| 1 | mushroom | 3.400 | 1.027–11.255 | 0.045 |
| 2 | lemon | 4.857 | 1.430–16.497 | 0.011 |
| 3 | vinegar | 2.280 | 0.630–8.248 | 0.210 |
| 4 | lavender | 7.600 | 2.071–27.895 | 0.002 |
| 5 | citronella | 7.856 | 1.495–41.292 | 0.015 |
| 6 | clove | 7.600 | 2.071–27.895 | 0.002 |
| 7 | ether | 19.000 | 4.425–81.556 | <0.0001 |
| 8 | strawberry | 9.229 | 2.463–34.583 | 0.001 |
| 9 | gas | 1.970 | 0.622–6.235 | 0.25 |
| 10 | mint | 5.000 | 1.448–17.271 | 0.011 |
| 11 | pine | 4.200 | 1.228–14.365 | 0.02 |
| 12 | salmon | 8.272 | 1.937–35.334 | 0.004 |

**Table 4** Spearman rank order correlation (values corrected for ties) between olfactory scores and demographic and clinical variables in PD patients

| Variables | Intensity | | Pleasantness | | Familiarity | | Edibility | | Identification | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ρ | *P* | ρ | *P* | ρ | *P* | ρ | *P* | ρ | *P* |
| Sex | –0.07 | NS | –0.18 | **0.003** | –0.09 | NS | –0.24 | **<0.001** | –0.02 | NS |
| Age | –0.26 | **<0.001** | –0.13 | **0.036** | –0.25 | **<0.001** | –0.06 | NS | –0.13 | **0.029** |
| Disease duration | –0.00 | NS | –0.05 | NS | 0.12 | **0.041** | –0.05 | NS | 0.01 | NS |
| Hoehn and Yahr score | –0.03 | NS | –0.20 | **<0.001** | –0.12 | **0.013** | –0.22 | **<0.001** | 0.02 | NS |
| UPDRS score | 0.03 | NS | –0.01 | NS | 0.09 | NS | 0.02 | NS | 0.08 | NS |
| L-Dopa dose | 0.06 | NS | –0.13 | **0.031** | –0.05 | NS | –0.07 | NS | –0.02 | NS |

Significant results are shown in bold.

striatal dopamine re-uptake sites in recent studies, assessed by means of single-photon-emission computed tomography (Lehrner *et al.*, 1995; Wolters *et al.*, 2000). The large olfactory impairments demonstrated in the current study cannot therefore be explained only by these neurochemical dysfunctions. The severe olfactory deficits found in our study could alternatively be explained by a recent finding demonstrating that olfactory dysfunction in PD is to some extent a sniffing impairment (Sobel *et al.*, 2001).

Since the odour identification task is also associated with severe impairments, one can suggest that olfactory dysfunction could also partly result from semantic processing impairment (Gurda and Oliveiraa, 1996; Watters and Patel, 2002). Identification impairments were not restricted to any particular subset of odorants, but were absent for stimuli inducing trigeminal perception such as vinegar and gas so confirming the results of previous electrophysiological studies (Kobal and Hummel, 1991; Hummel *et al.*, 1993; Hawkes *et al.*, 1997).

From the above we can summarize that the olfactory impairments observed in our tasks may be explained by a simultaneous injury of the olfactory areas situated in the temporal lobes and of neural substrates related to the sniffing activity, but also by an injury of the frontal areas involved in perceptual and semantic processes. In a recent cerebral imaging study, we showed that the emotional response to odours involves a neural network including not only the amygdala, the hypothalamus and the temporal pole, but also the orbitofrontal cortex and the superior frontal gyrus (Royet *et al.*, 2000). In two other studies, we further found that the task of odour familiarity judgement specifically induced an activation of the right orbitofrontal area, whereas the odour pleasantness judgement induced a corresponding activation of the left hemisphere (Royet *et al.*, 1999, 2001a). Odour processes seem thus lateralized, since the relative level of activation in the right and left orbitofrontal cortices were found to be dependent on the type of olfactory judgement. In the present study, we could not, however, ascribe specific brain localization to these olfactory deficits since all olfactory tasks showed an equal level of impairment.

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